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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 12 MAY 2004
WIPO PCT

Applicant's or agent's file reference YCT-765	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP 03/00203	International filing date *(day/month/year)* 14.01.2003	Priority date *(day/month/year)* 11.01.2002
International Patent Classification (IPC) or both national classification and IPC C07H17/08		
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 24 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.05.2003	11.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer de Nooy, A Telephone No. +31 70 340-2338

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

2, 8, 12, 14, 15, 17-21, 23, 26, 28-32, 34	as originally filed
1, 3, 4, 5, 6, 7, 9, 10, 11, 13, 16, 22, 24, 25, 27, 33, 35, 36, 37	received on 11.08.2003 with letter of 07.08.2003

Claims, Numbers

1-18	as originally filed

Claims, Pages

43, 44	received on 11.08.2003 with letter of 07.08.2003

Drawings, Sheets

1-11	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   - ☐ complied with.
   - ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   - ☒ all parts.
   - ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18

No: Claims

2. Citations and explanations

see separate sheet

Re Item IV

Lack of unity of invention

1. According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".
This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".

2. The feature which claims 1 and 2 have in common is a hemifumarate salt of the compound of formula I of claim 1.

3. Reference is made to the following documents:

D1: EP0643068
D2: EP0846697

Those documents disclose a hemifumarate salt of formula I of claim 1 (D1 example 57; D2 compound VII), which consequently cannot be the special technical feature which links together the seperate inventions of the application. Since there are no other features which may constitute the special technical feature, there is a lack of unity.

4. Although there is a lack of unity, examination is complete for the application.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

Documents D1 (example 57) and D2 (compound VII) disclose the fumarate salt of the compound of formula (I) of claims 1-3 as a crystal. However, the X-ray diffraction pattern of those crystals is different from the ones of claims 1-3 (see also page 8, lines

8-10 of the present description). Thus, claims 1-18 are novel in the sense of Article 33(2) PCT.

Inventive step

Document D2, which is considered to represent the most relevant state of the art, discloses the fumarate salt of the compound of formula I of claim 1 (D2: examples 6-10) from which the subject-matter of claims 1-18 differs in that crystals are obtained in the present application which show different X-ray diffraction patterns.

The technical effect of this difference is not known.

The problem to be solved by the present invention may therefore be regarded as the provision of different cristalline forms of the fumarate salt of the compound of formula I of claim 1.

The solution proposed in claims 1-18 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

Merely providing alternative forms of a crystal does not present any inventive step. Nor are there shown any unexpected effects for those cristalline forms. This lack of inventive step is also clear from the way claims 4-18 are drawn up. Those claims miss essential features explaining how the various cristalline forms are prepared. If the applicant is of the opinion that no such essential features are necessary in those claims, the processes must be obvious and consequently must be lacking an inventive step.

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DESCRIPTION

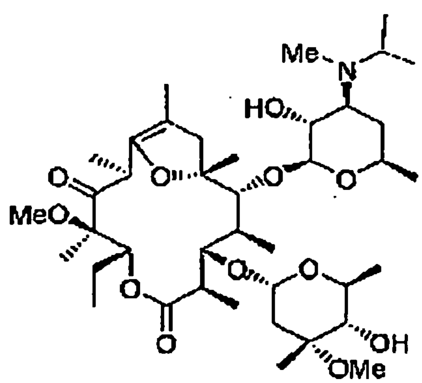
ANHYDRATE/HYDRATE OF AN ERYTHROMYCIN DERIVATIVE AND PROCESSES FOR PREPARING SAID ANHYDRATE/HYDRATE

Technical Field

The present invention relates to a novel hemifumarate crystal, anhydrate and X-hydrate of an erythromycin derivative as well as processes for preparing said anhydrate and X-hydrate, which are useful as pharmaceutical and therapeutic agents.

Background Art

The compound of formula (I):



(I)

(N-demethyl-N-isopropyl-12-methoxy-11-oxo-8,9-anhydroerythromycin A-6,9-hemiacetal) is described in JPA (Japanese Patent Publication for Laying-open) 1994-56873 (WO93/24509), JPA 1997-100291 (WO97/06177), etc., and known to have the effect of promoting gastrointestinal motility.

Processes for preparing this compound are described in JPA 1997-100291, Bioorg. & Med. Chem. Lett. Vol. 4, No. 11, p. 1347, 1994, etc.

Fumarate crystals of the compound of formula (I) are known in the art and have been designated Crystal form A, Crystal form C, and Crystal form D and can be obtained by the processes described in JPA 1997-100291.

Crystal form A can be obtained by recrystallizing a fumarate of the compound of formula (I) in an alcoholic solvent such as a mixed solvent of methanol and isopropanol in a molar ratio of the compound of formula (I) to the fumarate of 2:1.

Crystal form C can be obtained by treating a fumarate of the compound of formula (I) with ethyl acetate in a molar ratio of the compound of formula (I) to the

AMENDED SHEET

Cu-Kα radiation (hereinafter referred to as Crystal form D anhydrate).

The present invention also relates to a hemifumarate X-hydrate of the compound of formula (I) above characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1° and 14.2° but not showing a strong X-ray diffraction peak at a diffraction angle $2\theta = 13.5°$ as measured by X-ray diffractometry using Cu-Kα radiation (hereinafter referred to as Crystal form D X-hydrate).

The present invention also relates to a process for preparing Crystal form D X-hydrate comprising conditioning Crystal form D anhydrate by methods known in the art, such as by storing it in a humidifying room or spraying it with humidifying steam.

The present invention also relates to a process for preparing Crystal form D anhydrate comprising obtaining it via Crystal form F.

The present invention also relates to a process for preparing Crystal form D X-hydrate comprising obtaining it through Crystal form F.

The present invention also relates to a process for preparing Crystal form D X-hydrate comprising conditioning Crystal form D anhydrate obtained through Crystal form F.

The present invention relates to a hemifumarate crystal of a compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°.

The present invention also relates to a hemifumarate crystal of a compound of formula (I) above containing acetone and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation.

The present invention also relates to a hemifumarate crystal of a compound of formula (I) above containing methylethylketone and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation.

The present invention also relates to a hemifumarate crystal of a compound of formula (I) above containing tetrahydrofuran and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation.

The present invention also relates to a process for preparing a hemifumarate X-hydrate of a compound of formula (I) above showing strong X-ray diffraction peaks at

diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°, to obtain said hydrate.

The present invention also relates to a process for preparing a hemifumarate X-hydrate of a compound of formula (I) above containing acetone and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the compound of formula (I) above characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°, to obtain said hydrate.

The present invention also relates to a process for preparing a hemifumarate X-hydrate of a compound of formula (I) above containing methylethylketone and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°, to obtain said hydrate.

The present invention also relates to a process for preparing a hemifumarate X-hydrate of a compound of formula (I) above containing tetrahydrofuran and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°, to obtain said hydrate.

The present invention also relates to a process for preparing a hemifumarate anhydrate of a compound of formula (I) above characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1°, 13.5° and 14.2°, said process comprising the step of obtaining said anhydrate by treating a hemifumarate crystal of Crystal form G, G1, G2 or G3.

The present invention also relates to a process for preparing a hemifumarate X-hydrate of a compound of formula (I) above characterized by 2-theta angle positions in

the powder X-ray diffraction pattern of showing strong X-ray diffraction peaks at diffraction angles $2\theta = 7.1°$ and 14.2°, said process comprising the step of obtaining said hydrate by treating a hemifumarate crystal of Crystal form G, G1, G2 or G3.

The present invention also relates to a process for preparing a hemifumarate X-hydrate of a compound of formula (I) above characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1° and 14.2°, said process comprising the step of treating a hemifumarate anhydrate of the compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1°, 13.5° and 14.2°, wherein said anhydrate is obtained by treating a hemifumarate crystal of Crystal form G, G1, G2 or G3.

Brief Description of Drawings

Fig. 1 shows an example of a powder X-ray diffraction pattern of Crystal form F.

Fig. 2 shows an example of a powder X-ray diffraction pattern of Crystal form D anhydrate.

Fig. 3 shows an example of a powder X-ray diffraction pattern of Crystal form D X-hydrate.

Fig. 4 shows an example of measured results of moisture absorption isotherms of Crystal form D anhydrate and Crystal form D X-hydrate.

Fig. 5 shows a representative XRPD pattern of Crystal form G1.

Fig. 6 shows a representative XRPD pattern of Crystal form G2.

Fig. 7 shows a representative XRPD pattern of Crystal form G3.

Fig. 8 shows DSC and TGA curves of Crystal form G1.

Fig. 9 shows a TGA desolvation curve of Crystal form G1.

Fig. 10 shows a TGA desolvation curve of Crystal form G2.

Fig. 11 shows IR spectra of Crystal form G2 volatiles.

Fig. 12 shows a TGA desolvation curve of Crystal form G3.

Fig. 13 shows IR spectra of Crystal form G3 volatiles.

Best Mode for Carrying Out the Invention

Crystal form F of the present invention is characterized by the diffraction pattern as shown in Fig. 1 as measured by X-ray diffractometry using Cu-Kα radiation. As shown in Fig. 1, it is characterized by 2-theta angle positions in the powder X-ray

diffraction pattern of 6.6° and 8.5°. More specifically, it is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 6.6°, 8.5°, 16.6°, 20.8° and 23.5°.

Crystal form D anhydrate of the present invention is characterized by 2-theta angle positions in the powder X-ray diffraction pattern as shown in Fig. 2 as measured by X-ray diffractometry using Cu-Kα radiation. As shown in Fig. 2, Crystal Form D anhydrate is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1°, 13.5° and 14.2°. More specifically, it is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of7.1°, 9.4°, 10.2°, 12.3°, 13.5°, 14.2° and 16.1°. Among such chracteristic angle positions, the angle position of 13.5° is a characteristic angle position that is not found in crystal form D X-hydrate.

Crystal form D X-hydrate of the present invention is characterized by 2-theta angle positions in the powder X-ray diffraction pattern as shown in Fig. 3 as measured by X-ray diffractometry using Cu-Kα radiation, wherein X in X-hydrate is at about 1/2.

As shown in Fig. 3, Crystal form D hydrate is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1° and 14.2°, but does not show a X-ray diffraction peak at a diffraction angle $2\theta = 13.5°$ (the strong peak at a diffraction angle $2\theta = 13.5°$ found in Crystal form D anhydrate is not present). More specifically, it is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1°, 10.7°, 14.2°, 15.7° and 16.7°.

Crystal form G1 of the present invention is characterized by 2-theta angle positions in the powder X-ray diffraction pattern as shown in Fig. 5 as measured by X-ray diffractometry using Cu-Kα radiation. As shown in Fig. 5, the crystal form G1 is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°. More specifically, it is characterized by containing acetone and having 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°.

Crystal form G2 of the present invention is characterized by 2-theta angle positions in the powder X-ray diffraction pattern as shown in Fig. 6 as measured by X-ray diffractometry using Cu-Kα radiation. As shown in Fig. 6, the crystal form G2 is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°. More specifically, it is characterized by containing

methylethylketone and having 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°.

Crystal form G3 of the present invention is characterized by 2-theta angle positions in the powder X-ray diffraction pattern as shown in Fig. 7 as measured by X-ray diffractometry using Cu-Kα radiation. As shown in Fig. 7, the crystal form G3 is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°. More specifically, it is characterized by containing tetrahydrofuran and having 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°.

The X-ray diffraction angles described above can be measured with various commercially available equipments such as powder X-ray diffractometers using Cu-Kα radiation as well as other detection methods known in the art, or the like methods. The principle of powder X-ray diffractometry is described in detail at B614-B619 of the Practical Guide of the 14th revision of Pharmacopoeia of Japan (published by Hirokawa Publishing Co., 2001) or the like, and an error of diffraction angle on the order of ±0.2° is normally permissible.

Next, the present invention is specifically explained.

Crystal form F of the present invention can be prepared from Crystal form E, for example. Crystal form E means a hemifumarate of the compound of formula (I) above characterized by containing tetrahydrofuran and having 2-theta angle positions in the powder X-ray diffraction pattern of 5.6° and 10.4° as measured by X-ray diffractometry using Cu-Kα radiation.

Crystal form E can be obtained by treating Crystal form C at 20-40 °C in a mixed solvent of ethyl acetate and water. Crystal form C here can be used after isolation or preferably in suspension in the solvent. For example, Crystal form C is preferably obtained by treating Crystal form A with ethyl acetate and water is added to this suspension of Crystal form C in ethyl acetate.

The ratio of ethyl acetate to water in the mixed solvent of ethyl acetate and water used for suspension is normally from about 99:1 to about 95:5, preferably from about 97:3 to about 95:5. The temperature for suspension is normally from about 20 to about 40 °C, preferably from about 20 to about 30 °C. At temperatures of less than about 20 °C, the tendency is for Crystal form E or a mixture of Crystal forms C and E to transition into Crystal form D. The suspension period is normally from about 30 to

from the Crystal form D. Crystal form D anhydrate or Crystal form D X-hydrate here is preferably indirectly contacted with a mixed solvent of ethyl acetate and water by placing it in an (preferably saturated) atmosphere containing such mixed solvent, preferably in a saturated atmosphere. The atmosphere here is preferably an inert gas such as air, nitrogen, carbon dioxide or argon.

Crystal form F that is obtained as described above is dried under reduced pressure, for example, to give Crystal form D anhydrate of the present invention. The drying temperature here is preferably from about 20 to about 70 °C. Crystal form D anhydrate of the present invention can also be obtained by drying Crystal form D X-hydrate described below. However, this Crystal form D anhydrate must be stored under conditions resisting moisture absorption (i.e., resisting transition into Crystal form D X-hydrate) due to its hygroscopic nature such that it is partially or totally transferred into Crystal form D X-hydrate by adsorbing water in the atmosphere if it remains in normal atmosphere.

Crystal form D anhydrate of the present invention can also be obtained by drying Crystal form G1-, G2-, or G3 under reduced pressure. Thus obtained Crystal form D anhydrate may be conditioned by a known method such as leaving it in a humidifying steam room or spraying it with humidifying steam, to give Crystal form D X-hydrate.

Crystal form D X-hydrate of the present invention can be prepared, for example, by conditioning Crystal form D anhydrate described above by methods known in the art, such as by storing it in a humidifying steam room or spraying it with humidifying steam. Specifically, it can be prepared by conditioning Crystal form D anhydrate using a commercially available apparatus such as an air-circulating dryer or vibro-fluidized bed apparatus, for example. The atmosphere during conditioning is preferably an inert gas such as air, nitrogen, carbon dioxide and argon.

The transition point from Crystal form D anhydrate into Crystal form D X-hydrate is a relative humidity of about 30 % RH to about 40 % RH at about 25 °C, and the transition point from Crystal form D X-hydrate into Crystal form D anhydrate is a relative humidity of about 30 % RH to about 20 % RH at about 25 °C. Either transition readily occurs, specifically within a short period of about 10 minutes or less on a small scale. To ensure transition, it is preferable to maintain Crystal form D anhydrate at a relative humidity of 20 % RH or less at 25 °C and Crystal form D X-hydrate at a relative humidity of about 40 % RH or more at about 25 °C. Each of the transition

points tends to shift to low humidity side at temperatures lower than 25 °C and to high humidity side at temperatures higher than 25 °C.

The residual solvent (ethyl acetate) level decreases as Crystal form D anhydrate transitions into Crystal form D X-hydrate. Crystal form D X-hydrate is more stable than Crystal form D anhydrate. Moreover, Crystal form D X-hydrate is advantageous for industrial production because it is more easily handled than Crystal form D anhydrate. For these reasons, Crystal form D X-hydrate of the present invention is especially useful as a pharmaceutical material.

Crystal form D anhydrate of the present invention is useful as a material or an intermediate for the synthesis of this Crystal form D X-hydrate.

Crystal form F of the present invention is useful as a material or an intermediate for the synthesis of these Crystal form D anhydrate and D-form - X-hydrate.

A hemifumarate anhydrate of Crystal form D is obtained through a hemifumarate crystal of Crystal form G1, G2 or G3.

The residual solvent level described above can be determined by a known method such as gas chromatography. Gas chromatography is described in detail at B98-B114 of the Practical Guide of the 14th revision of Pharmacopoeia of Japan (published by Hirokawa Publishing Co., 2001) or the like. The measurement error by gas chromatography is normally within about ±1 %.

Iso-structural solvate G-form crystals, namely, Crystal form G1, Crystal form G2 and Crystal form G3 of the present invention can be obtained by directly or indirectly contacting hydrate Crystal form D described below with a specific solvent as described below.

<u>Separation for stereoisomers</u>

Compounds of the present invention may exist as stereoisomers wherein, asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The terms "R" and "S" used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem., 1976, 45: 13-30. The present invention contemplates various stereoisomers and mixtures thereof and are specifically included within the scope of this invention. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution

are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

Separation for formulation

The present invention provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration. The term "pharmaceutically acceptable carrier," as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of one skilled in the art of formulations.

Further included within the scope of the present invention are pharmaceutical compositions comprising one or more of the compounds of formula (I-II) prepared and formulated in combination with one or more non-toxic pharmaceutically acceptable compositions. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative agents, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for

example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be

acceptable diluent or solvent such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. (United States Pharmacopoeia) and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and salicylic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays,

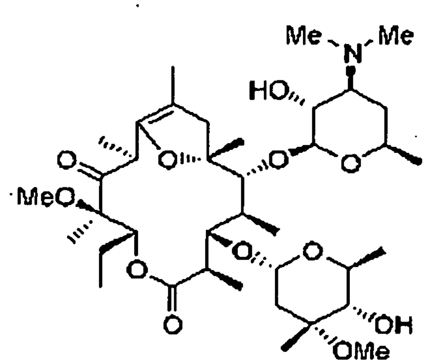
inhalants or patches. The active component is admixed under sterile conditions with a

by using a nuclear magnetic resonance spectrometer JNM-ECP500SS (made by JEOL) and only characteristic peaks were shown. Powder X-ray diffraction spectra were measured by using a powder X-ray diffractometer RINT-1100 (made by Rigaku). Residual solvent levels were measured by using a gas chromatograph GC-17A (made by Shimadzu) within an error of about ± 1 %. The starting material Dihydroxy compound described below (compound 1) can be prepared according to the process described in JPA 1997-100241 or modifications thereof.

[Example 1] Preparation of Crystal form F of [2S, 4R, 5R, 8R, 9S, 10S, 11R, 12R]-9-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-4-methoxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(isopropylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-14(1)-ene-3,7-dione (E)-2-butenedioic acid salt (2:1) (Crystal form F)

(1) Synthesis of a Z compound (compound 2)

To Dihydroxy compound (compound 1) (15 kg) of the formula below:

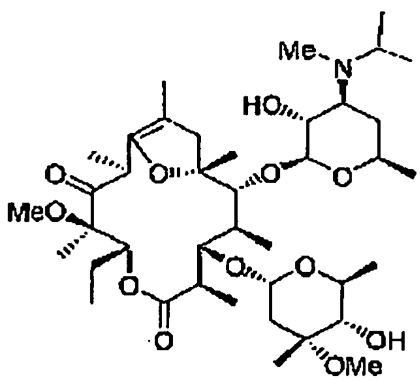


Compound 1

and sodium hydrogencarbonate (12.1 kg) was added ethyl acetate (67.7 kg). This mixed solution was heated to 55 °C and then stirred with benzyloxycarbonyl chloride (7.0 kg) for 1 hour. The mixed solution was further stirred with benzyloxycarbonyl chloride (31.6 kg) for 1 hour and then cooled to 28 °C, so that the starting Dihydroxy compound (compound 1) and the reaction intermediate (compound 1 added with a benzyloxycarbonyl group) were completely lost and converted into a Z compound (compound 2) of the formula below:

11R, 12R]-9-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl) oxy]-5-ethyl-4-methoxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(isopropylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-14 (1)-ene-3,7-dione (E)-2-butenedioic acid salt (2:1) (Crystal form D X-hydrate) by conditioning Crystal form D anhydrate

(1) Crystal form D anhydrate prepared according to the procedure of Example 2 (5.0 kg) was conditioned in an air-circulating dryer (made by Nippon Kansoki). This apparatus was fed with conditioning air at 18-20 °C, 55-68 %RH for 1 hour at a flow rate of 30 m^3/min. As a result, 4.9 kg (purity 99.50 %) of Crystal form D X-hydrate (moisture content: 2.4 %) of a hemifumarate of the compound of formula (I) below was obtained.



(I)

An example of the X-ray diffraction pattern of the resulting Crystal form D X-hydrate measured with Cu-Kα radiation is shown in Fig. 3. As apparent from Fig. 3, it showed strong peaks at diffraction angles 2θ = 7.1° and 14.2° but did not show a strong peak at a diffraction angle 2θ = 13.5° (the strong peak at a diffraction angle 2θ = 13.5° found in Crystal form D anhydrate has disappeared). More specifically, it showed characteristic peaks at diffraction angles 2θ = 7.1°, 10.7°, 14.2°, 15.7° and 16.7°.

This Crystal form D X-hydrate was easier to handle than Crystal form D anhydrate and therefore, advantageous in synthetic operation.

m.p.: 200.1 °C.

^{1}H-NMR (d_6-Acetone, ppm): 6.7 (1H, s, 1/2 (=<u>CH</u>-COOH)$_2$), 5.6 (1H, dd), 4.9 (1H, d), 4.6 (1H, d), 4.1 (1H, m), 3.4 (3H, s), 3.2-3.3 (2H, m), 3.0 (5H, m), 2.4-2.7 (6H, m), 1.1 (6H, m), 0.9 (3H, t).

Kα radiation was similar to that of Fig. 1 described in Example 1 (6) above.

[Example 6] Transition between Crystal form D anhydrate and Crystal form D X-hydrate depending on temperature conditions

Crystal form D anhydrate prepared according to the procedure described in Example 2 (100 mg) was changed to Crystal form D X-hydrate by increasing the relative humidity from 0 % RH to 90 % RH at 25 °C, and then Crystal form D X-hydrate was transferred into Crystal form D anhydrate by decreasing the relative humidity from 90 % RH to 0 % RH, and the moisture absorption isotherms were assessed. Measurements were made by using a dynamic moisture absorption meter DVS-1 (made by Surface Measurement Systems) at humidity points of every 2 % RH within the range of 16 % RH - 44 % RH and every 10 % RH elsewhere under the conditions of a threshold dt/ds < 0.002 and a threshold period = 3 hrs.

An example of the results is shown in Fig. 4. As shown in Fig. 4, a hysteresis loop was observed at 30 % RH - 40 % RH during increasing the relative humidity from 0 % RH to 90 % RH and at 30 % RH - 20 % RH during decreasing the relative humidity from 90 % RH to 0 % RH.

Powder X-ray diffraction analysis showed that the powder X-ray pattern changed before and after the hysteresis loop, confirming that the crystal form changed. Thus, the transition point from Crystal form D anhydrate into Crystal form D X-hydrate was situated at relative humidity 30 % RH - 40 % RH at 25 °C and the transition point from Crystal form D X-hydrate into Crystal form D anhydrate was situated at relative humidity 30 % RH - 20 % RH at 25 °C.

Powder X-ray diffraction analysis also confirmed that the crystal form was unchanged after the hysteresis loop (40 % RH or more) as shown by a constant powder X-ray pattern. Thus, the increase in moisture content after the hysteresis loop was thought to be due to the water of adhesion. If it is supposed that the increased moisture content in the hysteresis loop is crystal water, the value for X in X-hydrate was estimated at 1/2.

Each of the transition points above (hysteresis loop) tended to shift to low humidity side at temperatures lower than 25 °C and to high humidity side at temperatures higher than 25 °C.

[Example 7] Stability of Crystal form D anhydrate and Crystal form D X-hydrate

(1) Accelerated testing of Crystal form D anhydrate and Crystal form D X-hydrate at 40 °C for 1 month and at 60 °C for 1 month

Three lots of Crystal form D anhydrate prepared according to the procedure described in Example 2 were stored and dried under reduced pressure in a desiccator containing silica gel. After drying under reduced pressure, the desiccator was charged with air conditioned at a relative humidity of 0 % RH to perform accelerated testing of Crystal form D anhydrate at 40 °C for 1 month and at 60 °C for 1 month. Similarly, Crystal form D was stored in a desiccator conditioned at a relative humidity of about 75 % RH by an aqueous saturated sodium chloride solution to perform accelerated testing of Crystal form D X-hydrate at 40 °C for 1 month and at 60 °C for 1 month. Before and after accelerated testing, the crystal form was confirmed to be Crystal form D anhydrate or Crystal form D X-hydrate by powder X-ray diffraction spectra.

The resulting samples were tested for purity by HPLC, and the peak area of each sample was measured by automatic analysis to determine the product percentage by the area percentage method according to the equation below. The HPLC column used was YMC ODS AM303 (4.6 x 250 mm) with a mobile phase consisting of a solution of acetonitrile : water = 1:1 containing PICB-8 (Low UV) reagent, and a UV spectrometer (260 nm) and a PDA (200-400 nm) were used as detectors on 25 μL of each sample solution prepared by dissolving about 20 mg of each sample in a solution of acetonitrile : water = 1:1 to a volume of exactly 25 mL.

Degradants percentage (%) = (degradants peak area x 100) / (total of peak areas excluding peaks derived from fumaric acid and control solution)

An example of the results is shown in Table 1 below. All the lots showed that Crystal form D X-hydrate is more stable than Crystal form D anhydrate.

[Table 1. Percent Degradants Obtained for the Crystal Form D Anhydrate and Crystal Form D X-hydrate After Storage at Various Conditions]

		Lot 1	Lot 2	Lot 3
40 °C, 1 month	Anhydrate	1.01	1.38	1.41
	X-hydrate	0.17	0.42	0.22
60 °C, 1 month	Anhydrate	2.66	2.52	3.05
	X-hydrate	0.90	0.63	1.53

acetate) by gas chromatography. Before and after conditioning, the crystal form was confirmed by powder X-ray diffraction spectra to have been transferred from Crystal form D anhydrate into Crystal form D X-hydrate.

An example of the results is shown in Table 3 below. In all the lots, the residual solvent levels were lower in Crystal form D X-hydrate than Crystal form D anhydrate.

[Table 3 . Residual Solvent Levels for the Crystal Form D Anhydrate and Crystal Form D X-hydrate After Storage at Various Conditions]

	Conditioner	Conditioning conditions		Residual solvent level (ppm)
Lot A	Air-circulating dryer	20-21°C, 58-63%RH (air) 2 hrs	Anhydrate (Example 2)	697
			X-hydrate (Example 3(2))	636
Lot B	Vibro-fluidized bed dryer	22-28°C, 75±15%RH (nitrogen gas) 4 hrs	Anhydrate	616
			X-hydrate	446
Lot C	Fluidized bed granulator	24-29°C, 75±10%RH (air) 4 hrs	Anhydrate	750
			X-hydrate	424
Lot D	Vibro-fluidized bed dryer	19-26°C, 70-71%RH (nitrogen gas) 4 hrs	Anhydrate	875
			X-hydrate	424
Lot E	Air-circulating dryer	19-28°C, 41-71%RH (air) 72 hrs	Anhydrate	663
			X-hydrate	251

[Example 9] Preparation of Crystal form G1

Iso-Structural Crystal Form Gl.

Hydrate D-form crystal in an amount of 0.200 g was dissolved in 5.0 ml acetone, assisted with sonication, at ambient. The clear solution was filtered through a 0.2-um nylon filter. The filtrate was evaporated to dryness (1 day) in an open container at ambient temperature to allow the product to crystallize to give the hemifumarate salt as a variable hydrate-solvate.

[Example 10] Preparation of Crystal form G2

Iso-Structural Crystal Form G2.

Hydrate D-form crystal in an amount of 0.028 g was dissolved in 2.1 ml of methylethylketone, assisted with sonication, at ambient. The clear solution was filtered through a 0.2-um nylon filter. The filtrate was evaporated to dryness (4 days) in an open container at ambient temperature to allow the product to crystallize to give the hemifumarate salt as a variable hydrate-solvate.

[Example 11] Preparation of Crystal form G3

Iso-Structural Crystal Form G3.

Hydrate D-form crystal in an amount of 0.031 g was dissolved in 0.6 ml of tetrahydrofuran, assisted with sonication, at ambient. The clear solution was filtered through a 0.2-um nylon filter. The filtrate was evaporated to dryness (4 days) in an open container at ambient temperature to allow the product to crystallize to give the hemifumarate salt as a variable hydrate-solvate.

[Example 12] Characterization of Iso-Structural Solvate Crystal form G1, Crystal form G2 and Crystal form G3

The following experimental methods were adopted in order to characterize and identify each of Crystal form G1, Crystal form G2 and Crystal form G3 crystals.

a. Crystal form G1

Crystal form G1 was obtained from evaporative experiments with acetone. A representative XRPD (X-ray powder diffraction) pattern is shown in Figure 5. The XRPD pattern of Crystal form G1 is nearly identical to Crystal form G2 (methylethylketone) and Crystal form G3 (tetrahydrofuran). This may indicate that G1-G3-form materials are isostructural solvates. Additional characterization data obtained on Crystal form G2 and Crystal form G3 is provided in sections b and c below.

Thermal data for Crystal form G1 is plotted in Figure 8. The DSC (differential scanning calorimetry) curve exhibited multiple broad endothermic events occurring around 104 °C and an additional endothermic event exhibiting an onset temperature of 207 °C. The nature of these events was not confirmed by hot stage microscopy.

The TG (thermogravimetric) curve obtained on Crystal form G1 material shows a

weight loss of approximately 7.8% between 26 °C and 162 °C. The total weight loss corresponds to approximately 1.2 moles of acetone. A separate TG experiment (Figure 9) was done in order to determine if another form could be acquired through desolvation. Crystal form G1 was heated to 75 °C, providing a weight loss of approximately 7.0%. Weight loss in the TG data is observed to occur at or near the beginning of the experiment, indicating that some volatilization occurs

Crystal form G3 was obtained from evaporative experiments with tetrahydrofuran. A representative XRPD pattern is shown in Figure 7. The XRPD pattern of Crystal form G3 is nearly identical to Crystal form G1 and Crystal form G2. This indicates that Crystal form G3 is likely an iso-structural solvate of Crystal form G1 and Crystal form G2, obtained from acetone and methylethylketone, respectively (refer to sections a and b above).

A TG-IR experiment was done to determine the nature of the solvate and if another form could be acquired through its desolvation. Weight loss in the TG data (Figure 12) is observed to occur at or near the beginning of the experiment, indicating that some volatilization occurs under these conditions (dry helium flow). Based on these data, the TG weight loss may not provide an accurate measure of the solvation state of this material. Upon cooling to room temperature, this material was recovered and an XRPD pattern obtained. This pattern indicated conversion of Crystal form G3 material to a low crystalline or amorphous pattern. The IR spectra identify water and tetrahydrofuran as the volatiles removed during desolvation from ambient up to 63 °C and tetrahydrofuran as the volatile subsequently following (Figure 13). This indicates that Crystal form G3 is a mixed hydrate-solvate.

Based on the characterization data, Crystal form G3 appears to be a crystalline, hydrate-tetrahydrofuran solvate which is iso-structural with forms Crystal form G1 and Crystal form G2.

[Example 13] XRPD characterization of G-form crystal

Table 4 contains XRPD line positions of Form G. All four lines are required to be present, since the individual lines are observed in other forms. Line positions are rounded to the nearest 0.1 °2θ and reported as ± 0.2 °2θ. Table 5 contains the all of the experimental line positions for the same sample with relative intensities (I/Io) greater than 10 and in the range of 4 to 40 °2θ.

Table 4. Experimental XRPD Line Positions for Form G

Peak No.	2Theta[a]
1	5.4
2	10.4
3	10.7
4	12.1

a. Line positions rounded to the nearest 0.1 °2θ and reported as ± 0.2 °2θ.

Table 5. Experimental XRPD Peak List for Form G1 with Relative Initensity (I/Io) Greater than 10

Peak No.	2Theta[a]	I/Io[b]
1	4.2	30
2	4.5	28
3	4.7	30
4	4.9	34
5	5.4	68
6	5.9	24
7	6.1	21
8	6.5	24
9	6.9	21
10	7.3	20
11	7.5	19
12	7.9	23
13	8.2	18
14	8.4	18
15	8.7	17
16	9.0	19
17	9.2	19
18	9.4	19
19	9.8	37
20	10.1	38
21	10.4	72
22	10.7	100
23	11.1	34
24	11.7	33
25	12.1	75
26	12.5	34
27	12.9	24
28	13.2	19
29	13.5	22
31	14.3	15
33	15.1	12
36	16.2	13
41	17.9	29
42	18.5	13
45	19.7	24
47	20.5	12

a. XRPD line position rounded to the nearest 0.1 °2θ and reported as ± 0.2 °2θ.
b. Experimental relative intensities for comparison purposes only.

[Example 15] Utility of G Forms

Anhydrate Crystal form D Via Iso-Structural Crystal Form G2

Iso-structural Crystal form G2 crystal in an amount of 0.010 g was heated from ambient temperature to 165 °C under a constant purge of dry helium. The product was

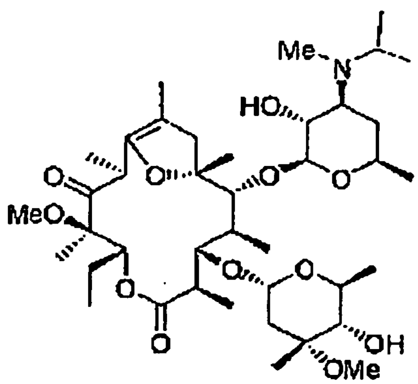
allowed to cool to ambient to give the hemifumarate salt as the anhydrate Crystal form D.

Industrial Applicability

Crystal form D X-hydrate of the present invention is especially useful as a pharmaceutical material because of the low residual solvent level, high stability even as a compound and easy handling. Crystal form D anhydrate of the present invention is useful as a material or an intermediate for the synthesis of this Crystal form D X-hydrate. Crystal form F of the present invention is useful as a material or an intermediate for the synthesis of these Crystal form D anhydrate and Crystal form D X-hydrate. The process for preparing Crystal form D X-hydrate by conditioning Crystal form D anhydrate according to the present invention is an inexpensive and simple process that can provide Crystal form D X-hydrate having stable quality.

containing tetrahydrofuran and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation.

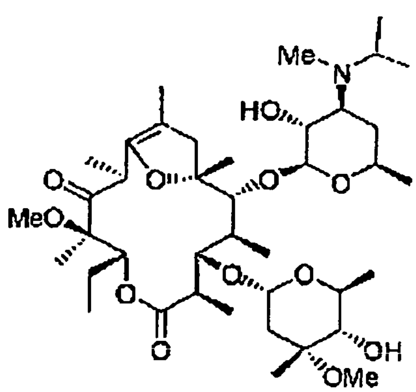
12. (Amended) A process for preparing a hemifumarate X-hydrate of a compound of formula (I):



(I)

showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°, to obtain said hydrate.

13. (Amended) A process for preparing a hemifumarate X-hydrate of a compound of formula (I):

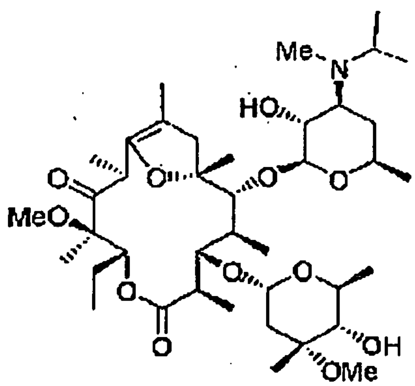


(I)

containing acetone and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the

compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°, to obtain said hydrate.

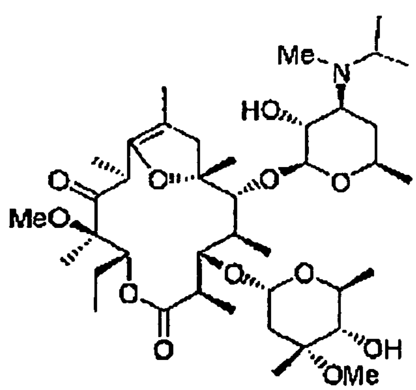
14. A process for preparing a hemifumarate X-hydrate of a compound of formula (I):



(I)

containing methylethylketone and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the compound of formula (I) characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°, to obtain said hydrate.

15. A process for preparing a hemifumarate X-hydrate of a compound of formula (I):



(I)

containing tetrahydrofuran and showing strong X-ray diffraction peaks at diffraction angles 2 theta = 5.4°, 10.4°, 10.7° and 12.1° measured by X-ray diffractometry using Cu-Kα radiation, said process comprising the step of treating a hemifumarate crystal of the compound of formula (I) characterized by 2-theta angle positions in the powder X-